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December 19, 2005

By Hand

Daniel Reisner, Esq.
Kaye Scholer, LLP
425 Park Avenue
New York, NY 10022-3598

Re: Pfizer v. Teva (CV 04-754 (JCL))

Dear Dan:

Enclosed are Teva's contention interrogatory responses. We have supplemented our responses to interrogatories 1, 3 and 5-7. We did not supplement our response to interrogatory 2 because we presently have nothing to add. We did not supplement our response to interrogatory 4, directed to contentions regarding secondary considerations, because such supplementation is premature prior to receiving Plaintiffs' responses to Teva's latest set of interrogatories, which seek, among other things, Plaintiffs' contentions regarding secondary considerations. We also did not supplement our responses to interrogatories 14, 16, 17 and 19, as we served responses to those interrogatories only ten days ago.

Sincerely,

Keith A. Zullow

KAZ/sr

cc: David D. DeLorenzi, Esq. (by overnight courier)

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA CORP., PHARMACIA & UPJOHN INC., PHARMACIA & UPJOHN COMPANY, G.D. SEARLE & CO., G.D. SEARLE LLC, SEARLE LLC (DELAWARE) and SEARLE LLC (NEVADA) Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. Defendant.	Civil Action No: 04-754 (JCL) **CONTAINS CONFIDENTIAL ATTORNEYS' EYES ONLY INFORMATION**

TEVA'S SECOND SUPPLEMENTAL RESPONSE
TO PFIZER'S FIRST SET OF INTERROGATORIES (NOS. 1, 3, AND 5-7)

Pursuant to Rules 26 and 33 of the Federal Rules of Civil Procedure and the Local Rules of the United States District Court for the District of New Jersey, Defendant Teva Pharmaceuticals USA, Inc. ("Teva") supplements to its responses to Pfizer's First Set of Interrogatories (Nos. 1, 3, and 5-7) as follows:

GENERAL OBJECTIONS

Teva incorporates by reference the general and specific objections originally set forth in Teva's Responses To Pfizer's First Set of Interrogatories (Nos. 1-12).

RESPONSES TO SPECIFIC INTERROGATORIES

Subject to and without waiving the foregoing General Objections, Teva responds as follows to Pfizer's interrogatories. These responses supplement Teva's previously provided responses, which Teva incorporates by reference.

INTERROGATORY NO. 1:

Notwithstanding Teva's allegations of invalidity in this matter, do Teva Celecoxib Capsules fall literally within the scope of any of the claims of the '823, '165, or '068 patents? If the response to this interrogatory is anything other than an unqualified admission, state each limitation of each of the claims of the '823, '165, or '068 patents that is not found in Teva's Celecoxib Capsules.

SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 1:

Teva's investigation is ongoing and the responses herein are based upon such information and documents as are reasonably available to Teva at this time and at this stage of the case. Subject to and without waiving its specific and General Objections, Teva responds as follows:

As to the '823 patent: The product that is the subject of Teva's ANDA No. 76-898 will not infringe at least claims 4-6, 10 and 12 of the '823 Patent. Claims 4-6, 10 and 12 of the '823 patent are directed to groups of compounds (or with respect to claim 10, a compound) that do not include celecoxib. The product that is the subject of Teva's ANDA No. 76-898 will not contain any active pharmaceutical compound other than celecoxib. Therefore, the product that is the subject of Teva's ANDA No. 76-898 will not literally infringe at least claims 4-6, 10 and 12 of

the '823 patent. Furthermore, Plaintiffs, in their interrogatory responses, have stated that they will not assert claims 4-6, 10 and 12 of the '823 patent. As to claims 1-3, 5-9, 11 and 13, which Teva understands to be the claims that Plaintiffs are asserting, Teva states that as set forth in response to Interrogatory 3,6 and 7, these claims are invalid and/or unenforceable, and there can be no infringement of an invalid claim or an unenforceable patent.

As to the '165 patent: The product that is the subject of Teva's ANDA No. 76-898 will not infringe at least claims 6-14 and 19-21 of the '165 patent. Claims 6-14 and 19-21 of the '165 patent are limited to compositions containing a therapeutically-effective amount of an active compound selected from a group of compounds that does not include celecoxib. The product that is the subject of Teva's ANDA No. 76-898 will not contain any active pharmaceutical ingredient other than celecoxib. Therefore, the product that is the subject of Teva's ANDA No. 76-898 will not literally infringe at least claims 6-14 and 19-21 of the '165 patent. Furthermore, Plaintiffs, in interrogatory responses, have stated that they will not assert claims 6-14 and 19-21 of the '165 patent. As to claims 1-5 and 15-18, which Teva understands to be the claims that Plaintiffs are asserting, Teva states that as set forth in response to Interrogatory 3,6 and 7, these claims are invalid and/or unenforceable, and there can be no infringement of an invalid claim or an unenforceable patent.

As to the '068 patent: The product that is the subject of Teva's ANDA No. 76-898 will not literally infringe any claims of the '068 patent. All of the claims of the '068 patent are limited to *methods* of using compounds to treat inflammation or an inflammation associated disorder. Teva does not, and will not practice such methods. Therefore, Teva's "Celecoxib Capsules" do not "fall literally within the scope" of any of the claims of the '068 patent.

Furthermore, Plaintiffs, in interrogatory responses, have stated that they will not assert claims 5-10 and 18 of the '068 patent. As to claims 1-4 and 11-17 of the '068 patent, which Teva understands to be the claims that Plaintiffs are asserting, Teva states that as set forth in response to Interrogatory 3,6 and 7, these claims are invalid and/or unenforceable, and there can be no infringement of an invalid claim or an unenforceable patent.

INTERROGATORY NO. 3:

For each claim, if any, of the '823, '165, or '068 patents, which Teva contends is obvious under 35 U.S.C. § 103, identify the combination of prior art that renders the claim obvious, describe the teaching of each reference which Teva contends should be combined with others to render the claim obvious, and explain how the prior art is combined and why it would be combined in order to render the claim obvious.

SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 3:

Teva objects to this interrogatory as premature in that it seeks Teva's contentions before discovery has ended. Teva further objects to this interrogatory as premature, overbroad and unduly burdensome because the parties have not exchanged their proposed construction of the claims. Teva further objects to this interrogatory as premature to the extent it seeks expert discovery which has not yet begun. Teva's investigation is ongoing and the responses herein are based upon such information and documents as are reasonably available to Teva at this time. Subject to and without waiving its specific and General Objections, and in addition to Teva's previous responses, Teva responds as follows:

An invention can be found obvious when the motivation to modify the prior art came from the problem to be solved. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665 (Fed. Cir. 2000).

In the 1993 time-frame, a person of ordinary skill in the art would have wanted to solve the problem of finding Cox-2 selective anti-inflammatory compounds with reduced gastrointestinal ("GI") side-effects, that were not covered by existing patents. As set forth below, based on the information available in the prior art to the person of ordinary skill, the compounds of at least the asserted claims[1] of the patents-in-suit, including those covering celecoxib, would have been obvious to a person of ordinary skill in the art. One of skill in the art would have had the motivation to combine information in the art to arrive at the compounds, compositions, and methods of treating inflammation as recited in the asserted claims of the patents-in-suit.

Information That Would Have Been Available To A Person Of Ordinary Skill In The Art

A. The Galbraith Presentation

On January 11, 1992, William Galbraith gave a presentation entitled: "DuP 697 As An Agent Which May Be A Selective Cyclooxygenase Inhibitor" ("the Galbraith Presentation") at the 1992 Winter Prostaglandin Conference in Keystone, Colorado. During a United Kingdom proceeding between Monsanto Company et al. and Merck and Company, Inc. et al., Mr. Galbraith provided a witness statement describing the information he disclosed during his presentation ("the Galbraith Witness Statement"), attached as Exhibit A. The Galbraith presentation disclosed test results of DuP 697, a diphenyl heterocycle having a five-membered central ring (a "6-5-6 compound"), in which one of the phenyls has a para-methylsulfone substituent and the other phenyl has a para-fluoro substituent.

[1] We understand Plaintiffs to have asserted claims 1-3, 7-9, 11 and 13 of the '823 patent; claims 1-5, and 15-18 of the '165 patent; and claims 1-4 and 11-17 of the '068 patent. Reference herein to the "asserted claims" refers to the aforementioned claims.

The Galbraith presentation disclosed that DuP 697 was anti-inflammatory, had an improved GI safety profile, and had characteristics that a person of ordinary skill in the art would have understood reflected Cox-2 selectivity.

B. U.S. Patent No. 5,474,995 ("The '995 Patent")

The '995 patent, assigned to Merck Frosst Canada, Inc. issued December 12, 1995 from Application Serial Number 179,467, filed January 10, 1994, which was a continuation-in-part of Application Serial Number 82,196 ("the '196 application"), filed June 24, 1993. Therefore, the '995 patent is prior art to the patents-in-suit under Section 102(e). The '995 patent includes all of the disclosure of the '196 application. The '196 application discloses specific Cox-2 selective compounds, and a genus of Cox-2 selective compounds, that will be anti-inflammatory with reduced GI side effects. The '995 patent discloses the Cox-2 selectivity of numerous heterocyclic classes of 6-5-6 diphenyl heterocycles having adjacent phenyl rings with one of those rings having a para-methylsulfone or a para-sulfonamide substituent. The '196 application does not expressly disclose, but does not teach away from, pyrazoles.

C. European Patent Application 0554829 A2 ("The '829 Application")

The '829 application, published on August 11, 1993, discloses diphenyl pyrazoles with para-methylsulfonyl substitution on one of the phenyl rings. The '829 application also teaches the use of pyrazoles with CF_3 substitution at the 3 position of the pyrazole ring. The '829 application teaches that such compounds are useful to treat inflammation and other conditions associated with inflammation where "cyclooxygenase products are a factor." The '829 application also teaches that such compounds would be useful for treating conditions only suitable for compounds showing reduced gastric side effects, *i.e.*, ulcerative colitis.

D. U.S. Patent No. 5,134,142 ("The '142 Patent")

The '142 patent issued on July 28, 1992, and discloses diphenyl pyrazoles with para-methylsulfonyl substitution on one of the phenyl rings. The '142 patent also teaches the use of pyrazoles with CF_3 substitution at the 3 position of the pyrazole ring. The '142 patent teaches that such compounds are useful to treat inflammation and other conditions associated with inflammation where "cyclooxygenase products are a factor." The '142 patent also teaches that such compounds would be useful for treating conditions only suitable for compounds showing reduced gastric side effects, *i.e.*, ulcerative colitis.

E. U.S. Patent No. 3,437,305 ("The '305 Patent")

The '305 patent issued in 1969 and discloses diphenyl pyrroles with para-sulfonamide substitution on one of the phenyl rings. The '305 patent teaches that such compounds are anti-inflammatory.

F. Canadian Patent No. 1,130,808 ("The '808 Patent")

The '808 patent issued in 1982 and discloses anti-inflammatory diphenyl pyrazoles having reduced side effects. Gastrointestinal side effects were known as the most common side effects of anti-inflammatories. The '808 patent teaches the use of a phenyl ring with para-methyl, para-methoxy or para-chloro substitution.

G. International Application No. PCT/JP 91/00744 ("The '744 PCT Application")

The '744 PCT application published on December 26, 1991 and discloses diphenyl thiophenes, in which one of the phenyls has a para-methylsulfone substituent. The '744 PCT application teaches that such compounds are useful to treat inflammation and other conditions associated with inflammation where "cyclooxygenase products are a factor." The '744 PCT

application also teaches that such compounds would be useful for treating conditions only suitable for compounds showing reduced gastric side effects, *i.e.*, ulcerative colitis.

Obviousness Of The Asserted Claims Of The '823 Patent

At least claims 1-3, 7-9, 11 and 13 of the '823 patent are invalid under 35 U.S.C. Section 103 because they are obvious in view of one or more of the references identified above. One of ordinary skill in the art would have been motivated to combine one or more of these references at least because: (1) they are all in the field of anti-inflammatories; (2) they all disclose 6-5-6 diphenyl heterocycles for use as anti-inflammatories; (3) they all disclose the use of para-methylsulfone or para-sulfonamide substitution to one of ordinary skill in the art; and (4) they either explicitly state that the disclosed compounds are Cox-2 selective or one of ordinary skill in the art would have understood there could be Cox-2 selectivity based on their disclosures and the general knowledge of one of ordinary skill in the art.

Obviousness Of The Asserted Claims Of The '165 Patent

At least claims 1-5 and 15-18 of the '165 patent are invalid under 35 U.S.C. Section 103 because they are obvious in view of one or more of the references identified above. The motivation to combine would be the same as set forth in regard to the '823 patent.

The '165 patent is also invalid under 35 U.S.C. Sections 101 and/or 103 for obviousness type double patenting over the '823 patent, because during prosecution of the '165 patent, Applicants failed to maintain consonance with the restriction requirements set forth during prosecution of the '823 patent.

Obviousness Of The Asserted Claims Of The '068 Patent

At least claims 1-4 and 11-17 of the '068 patent are invalid as obvious under 35 U.S.C. Section 103 because they are obvious in view of one or more of the references identified above. The motivation to combine would be the same as set forth in regard to the '823 patent.

The '068 patent is also invalid under 35 U.S.C. Sections 101 and/or 103 for obviousness type double patenting over the '823 and/or '165 patent, because during prosecution of the '068 patent, Applicants failed to maintain consonance with the restriction requirements set forth during prosecution of the '823 patent.

INTERROGATORY NO. 5:

For each claim, if any, of the '823, '165, or '068 patents, which Teva contends is invalid under 35 U.S.C. § 112, explain why each claim is alleged to be invalid for lack of adequate written description, lack of enablement, and/or failure to disclose the best mode of carrying out the invention.

SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 5:

Teva objects to this interrogatory as premature to the extent it seeks expert discovery, which has not yet begun, at this stage of the litigation. Teva's investigation is ongoing and the responses herein are based upon such information and documents as are reasonably available to Teva at this time. Subject to and without waiving its specific and General Objections, Teva responds as follows:

As to the '823 patent: At least claims 1-3, 7-9, 11 and 13 of the '823 patent are invalid under 35 U.S.C. Section 112 for failure to disclose the best mode of carrying out the invention, for at least the reasons set forth below.

The '823 patent was the result of work done in Searle's "Cox-2 Inhibitor" program. Within the Cox-2 inhibitor program, criteria existed for determining which compounds were preferred. These criteria included preferred levels of potency for the inhibition of the Cox-2 enzyme, preferred levels of selective inhibition of the Cox-2 enzyme as compared to the Cox-1 enzyme, and efficacy in a number of *in vivo* models, including: (1) the rat carrageenan paw edema model; (2) the Hargreaves model of inflammatory pain; and (3) the rat adjuvant arthritis model.

On or before November 30, 1993, one or more of the named inventors of the '823 patent had a preference for compounds that were potent and/or selective inhibitors of the Cox-2 enzyme as compared to the Cox-1 enzyme. These inventors believed that compounds which were potent and/or selective inhibitors of the Cox-2 enzyme would be anti-inflammatory with the potential for reduced side effects. In addition, one or more of the named inventors believed that the best compounds would be active in each of the identified *in vivo* models. Nonetheless, not all of these preferred characteristics of the claimed compounds were included in the '823 patent. The failure to disclose one or more of these inventor preferences constitutes a best mode violation, because such preferences would materially affect using the compounds of the invention "as inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects," as stated in the '823 patent. As a result, at least claims 1-3, 7-9, 11 and 13 are invalid under 35 U.S.C. Section 112.

As to the '165 patent: At least claims 1-5 and 15-18 of the '165 patent are invalid under 35 U.S.C. § 112 for failure to disclose the best mode of carrying out the invention for the same reasons set forth above for the '823 patent.

At least claims 1-5 and 15-18 of the '165 patent, if construed to encompass virtually any pharmaceutical composition containing the recited substituted pyrazolyl benzenesulfonamides, are invalid under 35 U.S.C. Section 112 for lack of adequate written description and for lack of enablement. Independent claims 1 and 15 include the limitations that the claimed pharmaceutical composition comprises a "therapeutically-effective amount of a compound and a pharmaceutically-acceptable carrier or diluent." Claims 2-5 and 16-18 depend either directly or indirectly from claims 1 or 15, and therefore contain these same limitations. Therefore, if the claims are construed to encompass any pharmaceutical composition containing the compounds listed, in amounts in a possible range of 0.01 mg to over 2000 mg, they would be invalid for lack of adequate written description and for lack of enablement. The narrower preferred ranges disclosed do not remedy this lack of written description or enablement for the reasons set forth below.

Nothing in the '165 patent shows that the applicants were "in possession" of a pharmaceutical composition containing a therapeutically-effective amount of the subject compounds as broadly as claimed. In fact, the specification, prosecution history and other evidence show that the applicants were not in possession of the alleged invention, as broadly as claimed, at the time the application was first filed. For example, the '165 patent does not explain how to achieve a "composition" containing a "therapeutically-effective" amount of the claimed compounds. At least claims 1-5 and 15-18 of the '165 patent do not even specify the recipient of the composition. The '165 specification provides no guidance as to how to achieve a composition containing a therapeutically-effective amount, and the claims are so broad as to also provide no guidance how to choose effective compositions within the broad ranges without complicated and laborious trial and error.

Moreover, at least claims 1-5 and 15-18 of the '165 patent do not meet the requirements of Section 112, first or second paragraph, because they do not recite: (1) a disease to be treated, (2) a rate of administration, (3) a numerical dosage range, (4) a dosage form or (5) a recipient of the composition. Therefore, at least claims 1-5 and 15-18 of the '165 patent are indefinite because they do not particularly point out and distinctly claim the subject matter which the applicants regard as their invention. In addition, because at least claims 1-5 and 15-18 of the '165 patent cover all pharmaceutical compositions containing the subject compounds, without further guidance or direction in the specification for therapeutic administration, either the claims should be restricted to the scope of the embodiments disclosed in the specification, or the claims are impermissibly broad. In either case, the broad scope of at least claims 1-5 and 15-18 of the '165 patent are neither adequately described nor adequately enabled by the '165 patent as required by 35 U.S.C. Section 112, first paragraph.

As to the '068 patent: At least claims 1-4 and 11-17 of the '068 patent are invalid under 35 U.S.C. Section 112 for failure to disclose the best mode of carrying out the invention for the same reasons set forth above for the '823 patent. These claims are also invalid under 35 U.S.C. Section 112, first or second paragraph, because the claims of the '068 patent do not recite (1) a rate of administration, (2) a numerical dosage range, (3) a dosage form or (4) a recipient of the composition, and because the specification provides inadequate guidance as to how to achieve a composition containing a therapeutically-effective amount.

INTERROGATORY NO. 6:

For each claim, if any, of the '823, '165, or '068 patents, which Teva contends is unenforceable due to a breach of the duty of candor as set forth in 37 C.F.R. § 1.56, identify the

material information allegedly known to Pfizer that was affirmatively misrepresented or not disclosed to the PTO, and explain why such information was allegedly material.

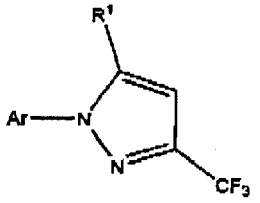
SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 6:

Teva objects to this interrogatory as premature in that it seeks Teva's contentions this early in discovery. Teva has not completed depositions of all of the inventors and prosecuting attorneys for the patents-in-suit. Teva further objects to this interrogatory as premature, overbroad and unduly burdensome because the parties have not exchanged their proposed construction of the claims. Teva further objects to this interrogatory as premature to the extent it seeks expert discovery which has not yet begun. Teva's investigation is ongoing and the responses herein are based upon such information and documents as are reasonably available to Teva at this time. Teva further objects to this interrogatory as vague and ambiguous to the extent that it asks Teva to "identify the material information allegedly known to Pfizer . . ." "Pfizer" has not been defined. Moreover, the patents-in-suit have been assigned (on their faces) to G.D. Searle & Co. Subject to and without waiving its specific and General Objections, Teva responds as follows:

As to the '823 patent: The March 23, 1995 ISR cited, *inter alia*, the following 6 references designated by the PCT examiner as type "X": (1) Mokhtar, H., *Synthesis of Nitrogenous Compounds, Part II*; (2) Mokhtar, H., *Synthesis of Nitrogenous Compounds from δ-Unsaturated 1,3-Dicarbonyl Esters. Part I. Substituted Pyrazoles, Isoxazoles and Oxyquinoxalines*; (3) Soliman, R., *et al.*, *Synthesis and Antidiabetic Activity of Some Sulfonylurea Derivatives of 3,5-Disubstituted Pyrazoles*; (4) European Patent No. 554,829; (5) U.S. Patent No. 4,146,721; and (6) Makki, M.S.I., *et al.*, Chem. Abstracts, 121:11 1994 (collectively "the non-disclosed ISR references").

Neither Mr. Bulock nor applicants disclosed the non-disclosed ISR references to the examiner of Application No. 160,594 (the "'594 application"). The non-disclosed ISR references were material to the prosecution of the '594 application for at least the following reasons: (a) international application PCT 94/12720 (the "'720 PCT application") and the '594 parent application are related, in that the '594 parent application is the grandparent of the '720 PCT application and all of the people identified as inventors of the '594 parent application are also identified as inventors of the '720 PCT application; (b) the '720 PCT application and the '594 parent application had similar claims; (c) the non-disclosed ISR references were cited in the March 23, 1995 ISR to the '720 PCT application; and (d) the non-disclosed ISR references were designated as type "X," meaning that according to the PCT Search Authority, when considered in isolation and without reliance on any other reference or the knowledge of a person in the relevant art at that time, the non-disclosed ISR references render unpatentable the claims of the related '720 PCT application.

Applicants and Mr. Bulock also failed to disclose the '808 patent to the Patent Office during prosecution of the '594 parent application. The '808 patent describes and claims compounds having the general structure:



In this structure, Ar signifies, *inter alia*, a substituted phenyl group. The '808 patent describes compounds that render obvious claims of the '594 parent application in view of one or more references identified in Teva's Supplemental Response to Interrogatory No. 3.

Mr. Bulock's knowledge of the '808 patent and its materiality is evidenced by at least the following: (a) Mr. Bulock's disclosure of the Matsuo '142 patent in a January 11, 1994 Information Disclosure Statement ("IDS"), noting that it disclosed 1,5, diaryl pyrazoles having anti-inflammatory activity; (b) the fact that Mr. Bulock reviewed the Matsuo '142 patent and determined it to be "pertinent" to the '594 parent application; (c) on information and belief, Mr. Bulock's recognition that the Matsuo '142 patent described the '808 patent as disclosing "pyrazole derivatives having anti-inflammatory and analgesic activities"; and (d) Mr. Bulock's description of the disclosure of the '808 patent in the application for U.S. Patent No. 5,475,018 submitted by him on November 30, 1993.

As to the '165 patent: This patent is unenforceable for the same reasons as set forth with regard to the '823 patent. In addition, defendant states that applicants and Mr. Bulock failed to disclose the '808 patent during prosecution of the '165 patent. The '808 patent describes compounds that anticipate and/or render obvious claims of the '059 divisional application in view of one or more references identified in Supplemental Response to Interrogatory No. 3. At least Mr. Bulock's knowledge of the '808 patent and its materiality is evidenced by at least the following: (a) Mr. Bulock's disclosure of the Matsuo '142 patent in a June 1, 1995 IDS, noting that it disclosed 1,5, diaryl pyrazoles having anti-inflammatory activity; (b) the fact that Mr. Bulock reviewed the Matsuo '142 patent and determined it to be "pertinent" to the '059 divisional application; (c) on information and belief, Mr. Bulock's recognition that the Matsuo '142 patent described the '808 patent as disclosing "pyrazole derivatives having anti-inflammatory and analgesic activities"; and (d) Mr. Bulock's description of the disclosure of the '808 patent in the application for U.S. Patent No. 5,475,018 submitted by him on November 30, 1993.

As to the '068 patent: Defendant states that applicants and Mr. Bulock failed to disclose U.S. Patent Application Ser. No. 08/949,922 (the "922 application") during prosecution of U.S. Patent Application Ser. No. 648,133 (the "113 CIP application"), from which the '068 patent issued. Claim 1 of the '922 application claims a method of treating a neoplasia with a genus of compounds that encompass celecoxib. As filed, claim 6 of the '922 application, claimed the following:

> The method of Claim 1 wherein the neoplasia is selected from colorectal cancer, gastrointestinal cancer . . .

Because of the overlapping subject matter of the '922 application and the '113 CIP application, the existence of the copending '922 application would have been material to the Examiner of the '113 CIP application with respect to issues of patentability and inventorship.

Applicants and Mr. Bulock also failed to disclose the '808 patent during prosecution of the '068 patent. The '808 patent describes compounds and uses of compounds that anticipate and/or render obvious the claims of the '113 CIP application in view of one or more references identified in Supplemental Response to Interrogatory No. 3. Mr. Bulock's knowledge of the '808 patent and its materiality is evidenced by at least: (a) Mr. Bulock's disclosure of the Matsuo '142 patent in the March 3, 1997 IDS, noting that it disclosed 1,5, diaryl pyrazoles having anti-inflammatory activity; (b) the fact that Mr. Bulock reviewed the Matsuo '142 patent and determined it to be "pertinent" to the '113 CIP application; (c) on information and belief, Mr. Bulock's recognition that it the Matsuo '142 patent described the '808 patent as disclosing "pyrazole derivatives having anti-inflammatory and analgesic activities"; and (d) Mr. Bulock's description of the disclosure of the '808 patent in the application for U.S. Patent No. 5,475,018 submitted by him on November 30, 1993.

Applicants also committed inequitable conduct with regard to the '068 patent by failing to disclose U.S. Patent No. 3,427,305 ("the '305 patent") to the Patent Office. The '305 patent is assigned to G.D. Searle & Co., one of the Plaintiffs, and issued in 1969. It discloses the use of diphenyl pyrrole compounds as anti-inflammatories, in which one of the phenyls has a para-sulfonamide substitution. As set forth above, the '823 patent indicates that use of a para-sulfonamide substituted phenyl, at least with diphenyl pyrazole compounds, is a distinguishing aspect of the invention as compared to use of para-methylsulfonyl substituted pyrazoles. In view of this, the '305 patent would have been material to examination of the patents-in-suit based on its disclosure of anti-inflammatory diphenyl pyrroles with a para-sulfonamide substituted phenyl.

In addition, the patents-in-suit are each unenforceable because during their prosecution, Applicants withheld WO 95/00501 ("the '501 PCT application"), a material reference.

The '501 PCT application was filed June 9, 1994, and identifies as a priority application, among others, U.S. Application Serial No. 082,196, filed June 24, 1993 (which issued, after a continuation-in-part, as U.S. Patent No. 5,474,995). Therefore, the '501 PCT application has a priority date earlier than the filing of the patents-in-suit.

The '501 PCT application published January 5, 1995, more than ten months before November 14, 1995 issuance of the '823 patent, the first of the patents-in-suit to issue. The '501 PCT application discloses the Cox-2 selectivity of numerous heterocyclic classes of 6-5-6 diphenyl heterocycles having adjacent phenyl rings with one of those rings having a para-methyl sulfone or a para-sulfonamide substituent.

The specification of the '823 patent states: "Pyrazoles have been described for use in the treatment of inflammation" and identifies as an example a diphenyl pyrazole with a para-methylsulfone substituted phenyl group. The specification goes on to state: "However

pyrazolyl-benzenesulfonamides have not been described as having such activity." Thus, the specification of the '823 patent indicates that a distinguishing aspect of the invention is the use of a phenyl having sulfonamide substitution rather than methylsulfone substitution. Therefore, the disclosure of the '501 PCT, *i.e.*, that both methylsulfones and sulfonamides can be used to achieve Cox-2 selectivity, would have been material to the Examiner of the patents-in-suit.

Applicants also committed inequitable conduct with regard to each of the patents-in-suit by failing to disclose DuP 697. One or more of the inventors listed on the patents-in-suit were aware of the prior art compound DuP 697 while those patent applications were being prosecuted. DuP 697 contained important phenyl substituents which conferred Cox-2 selectivity and/or potency as an anti-inflammatory, substituents that were similar to the phenyl substituents claimed in the pending applications for the patents-in-suit. During prosecution of the patents-in-suit, at least one of the inventors also understood that DuP 697 was an anti-inflammatory with an improved GI safety profile, and had characteristics that a person of ordinary skill in the art would have understood reflected Cox-2 selectivity. On information and belief, based on the information set forth above, at least one of the inventors of the patents-in-suit would have understood that DuP 697 was material to the patentability of the compounds, compositions, and methods of treating inflammation claimed in the applications for the patents-in-suit.

INTERROGATORY NO. 7:

For each claim, if any, of the '823, '165, or '068 patents, which Teva contends is unenforceable due to a breach of the duty of candor as set forth in 37 C.F.R. § 1.56, identify the information that demonstrates Pfizer's alleged intent to mislead the PTO, and explain how such information demonstrates an intent to mislead the PTO.

SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 7:

Teva objects to this interrogatory as premature in that it seeks Teva's contentions this early in discovery. Teva further objects to this interrogatory as premature, overbroad and unduly burdensome because the parties have not exchanged their proposed construction of the claims. Teva has not completed depositions of all of the inventors and prosecuting attorneys for the patents-in-suit. Teva further objects to this interrogatory as premature to the extent it seeks expert discovery which has not yet begun. Teva's investigation is ongoing and the responses herein are based upon such information and documents as are reasonably available to Teva at this time. Teva further objects to this interrogatory as vague and ambiguous to the extent that it asks Teva to "identify the information that demonstrates Pfizer's alleged intent . . .". "Pfizer" has not been defined. Moreover, the patents-in-suit have been assigned (on their faces) to G.D. Searle & Co. Subject to and without waiving its specific and General Objections, Teva responds as follows:

Teva incorporates its supplemental response to Interrogatory 6. In addition, Teva responds as set forth below:

As to the '823 Patent: On information and belief, at least Mr. Bulock knew about the non-disclosed ISR references referred to in Teva's Supplemental Response to Interrogatory No. 6 before the '594 parent application was issued as the '823 patent. Mr. Bulock's (and Applicants') knowledge of the materiality of the non-disclosed ISR references to a reasonable examiner is evidenced by at least the following: (a) Applicants' receipt the March 23, 1995 ISR designating the non-disclosed references as type "X," indicating that the PCT Search Authority considered the references material to the related PCT application; (b) Mr. Bulock's presumed knowledge of the standard for materiality under 37 C.F.R. § 1.56 and the standards set forth in

Section 2001.06(a) of the M.P.E.P regarding the strong inference that material references cited in a related PCT application are material; (c) Mr. Bulock's disclosure of the non-disclosed ISR references to the examiners of the '059 divisional application, indicating that by August 23, 1995, nearly three months prior to issuance of the '594 application, Mr. Bulock had reviewed the ISR references and determined that they were material to the patentability of claims in '059 divisional application which are similar to the claims of the '594 application; and (d) Mr. Bulock's disclosure of the ISR references to the examiner of U.S. Patent Application Ser. No. 08/223,629. Mr. Bulock did not disclose the non-disclosed ISR references to the examiner of the '594 parent application, nor did Applicants. Mr. Bulock's and Applicants' failure to disclose the non-disclosed ISR references during prosecution of the '549 parent application, despite knowledge of the references and their materiality, evidences an intent to deceive the Patent Office, and renders the '823 patent unenforceable due to inequitable conduct during its prosecution.

Likewise, Mr. Bulock's and applicants' failure to disclose the '808 patent during prosecution of the '594 parent application, despite knowledge of the patent and its materiality, evidences an intent to deceive the Patent Office, and renders the '823 patent unenforceable due to inequitable conduct during its prosecution.

One or more of the named inventors of the patents-in-suit and Mr. Bulock, who prosecuted the patents-in-suit, also knew about the '501 PCT application prior to issuance of the '823 patent, and on information and belief, knew of its materiality. Yet the '501 PCT application was never disclosed to the Examiners of the patents-in-suit during the prosecution of those patents. These facts evidence intent, on the part of the Applicants for the patents-in-suit, and Mr. Bulock, to deceive the Patent Office by withholding the '501 PCT application.

DuP 697 was a lead compound disclosing a 6-5-6 configuration which was the basis for Searle's research on COX-2 selective compounds leading to the compounds, compositions and methods claimed in the patents-in-suit. Applicants' failure to disclose this lead compound during prosecution of the patents-in-suit, despite knowledge of its materiality, evidences intent to deceive the Patent Office and renders each of the patents-in-suit unenforceable.

As to the '165 patent: Mr. Bulock's and applicants' failure to disclose the '808 patent, the '501 PCT application, and DuP 697 during prosecution of the '059 divisional application, despite knowledge of these references and their materiality, evidences an intent to deceive the Patent Office, and renders the '165 patent unenforceable due to inequitable conduct during its prosecution.

As to the '068 patent: Mr. Bulock and one or more of the inventors of the patents-in-suit knew about the '305 patent before issuance of the '068 patent. Nonetheless, the '305 patent was not disclosed to the Examiners of the '068 patent. This knowledge, and the materiality of the '305 patent, evidence intent to deceive the Patent Office on the part of Mr. Bulock and one or more of the inventors of the '068 patent.

Mr. Bulock's and applicants' failure to disclose the '808 patent, the '501 PCT application, the '305 patent, and DuP 697 during prosecution of the '113 application, despite knowledge of these references and their materiality, evidences an intent to deceive the Patent Office, and renders the '068 patent unenforceable due to inequitable conduct during its prosecution.

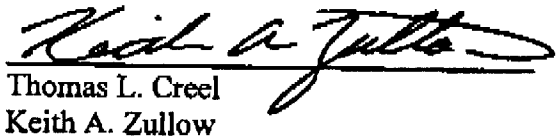
In addition, Mr. Bulock prosecuted both the '922 and the '113 CIP applications. Mr. Bulock's and applicants' failure to disclose the '922 application during prosecution of the '113 CIP application, despite knowledge of its materiality, evidences an intent to deceive the Patent

Office, and renders the '068 patent unenforceable due to inequitable conduct during its prosecution.

AS TO OBJECTIONS,

Dated: New York, New York
December 19, 2005

GOODWIN PROCTER LLP



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Attorneys for Defendant
Teva Pharmaceuticals USA, Inc.

EXHIBIT A

Defendants
W Galbraith
First
WG1-WG3
Dated: 23 August 1999

IN THE HIGH COURT OF JUSTICE

CH 1998 M No 1421

CHANCERY DIVISION

PATENTS COURT

BETWEEN

(1) MONSANTO COMPANY
(2) G.D. SEARLE & COMPANY
(3) PFIZER INC.

Claimants

- and -

(1) MERCK & CO., INC.
(2) MERCK SHARP & DOHME LIMITED

Defendants

FIRST WITNESS STATEMENT OF
WILLIAM GALBRAITH

I, WILLIAM GALBRAITH, of 78 Suomi Street, Paxton, Massachusetts, USA will say as follows:

1. I am an Assay Development Scientist in the Labware group of Becton Dickinson.

2. I obtained a B.A. in Chemistry from Western Reserve University, Cleveland, Ohio in 1966. I obtained a M.S. in 1968 and a Ph.D. in Biological Chemistry in 1971, from the University of Michigan.

3. From 1971 to 1979 I worked as a biochemist in the pharmacology department of Riker Laboratories, the pharmaceutical subsidiary of 3M Company, in Minnesota. During this time I developed *in vitro* screens and animal models for the mucolytic and anti-inflammatory programmes.

4. In 1979 I joined DuPont in Delaware, as a member of the pharmacology department in the pharmaceutical division. My main responsibility was to develop *in vitro* and *in vivo* assays to characterise the mechanism of action of anti-inflammatory molecules that were in clinical trials at the time.

Dup 697.

5. There was a series of anti-inflammatory compounds about ready for clinical trials when I joined DuPont. That was the diaryl-imidazole series with tiflamazole as the clinical candidate. The structure-activity studies around the tiflamazole led to DuP 697. The diaryl-imidazoles as exemplified by tiflamazole (EN350) proved to be potent cyclooxygenase inhibitors.

6. When DuPont expanded its pharmaceutical effort in 1981, I continued with the Inflammatory Diseases group. The major focus of the group was to find anti-inflammatories that worked by mechanisms other than inhibition of cyclooxygenase.

7. As the tiflamazole clinical studies went along, DuP 697 development was continued as a backup clinical candidate. It had a better safety profile in animal models than the compounds that were approved for use by patients. To help find compounds that might have a better safety profile, my lab developed cyclooxygenase assays from tissues such as brain and kidney. These tissues contain COX and its presence can be detected in these tissues by measuring the conversion of arachidonic acid to prostaglandins. DuP 697 was more effective at inhibiting COX in some tissues than others. These data were published in Gans et al., *Anti-Inflammatory and Safety Profile of DuP 697, a Novel Oral Effective Prostaglandin Synthesis Inhibitor* (1990) J Pharm.-Exp. Ther 180-187, 254. I refer to the copy of this paper that is marked "Exhibit WG 1".

Keystone Prostaglandin Conference

8. In January 1992, I attended the Keystone Prostaglandin Conference where I gave a presentation about the work on DuP 697. The title of the presentation was "DuP 697 As an Agent Which May Be A Selective Cyclooxygenase Inhibitor". As I recall from what I said during the presentation, my central theme was that DuP 697 acted like a potent cyclooxygenase inhibitor in some tissues but lacked such activity in others. To my knowledge, this was the first public disclosure of the cellular activities of DuP 697 in the LPS-induced monocyte and the IL-1 beta-induced fibroblast assays compared to the previously described lack of activity in the platelet systems which contain COX I. We now know that DuP 697's activity in the tissue is due to its COX-2 inhibitory activity. It was also the first time we compared its activity in these tissues to its lack of activity in platelet systems which contain the enzyme COX-1. At the time, cloned and expressed as COX II was not available to me, but the obvious experiment was to prove that the selective activity of DuP 697 was due to its inhibition of COX II because it was a poor inhibitor of COX I.

9. I still have a record of the slides I used at that conference. I refer to the copies of the slides upon which I made notes in preparation for the presentation I was to give that are marked "Exhibit WG 2". I also refer to the better copies of these slides that are marked "Exhibit WG 3". My presentation incorporated showing the slide explaining experimental design results and key-facts. The information I disclosed in relation to each slide is detailed below at paragraphs 10 to 20:

10. Slide 1, "DuP 697 Structure." I described DuP 697 as a non-acidic diaryl-bromo-thiophene that was very hydrophobic and said that the lack of an acidic function group may make it less likely to directly irritate the gastrointestinal tract.

11. Slide 2, "DuP 697 Metabolite". I mentioned that the conversion of the -bromo to a -methylsulfonyl was unusual and that in rats the half-life was 1 to 2 days for DuP 697 and its metabolite, but longer for the metabolite in dogs. The excretion was predominantly via the faeces.

12. Slide 3, "DuP 697 Anti-Inflammatory Activity". Then I switched to the animal pharmacology. I described the two rat models of arthritis on the slide and indicated that the major differences between the models was whether or not the arthritic-like condition was established before the drug was administered and that the drug was given for 7 days in the "established" model and for 14 days in the "non-established" model. The drugs were given orally and the inflammation was evaluated using the paw that was not injected with adjuvant. I described the DuP 697 as being equipotent with indomethacin and piroxicam in these models of chronic inflammation. For comparison, I mentioned that DuP 697 metabolite was about 1/3 as potent as the parent compound in this model.

13. Slide 4, "DuP 697 Analgesic Activity". On this slide I demonstrated the activity of DuP 697 in a model of inflammatory pain. I described the model which is pain resulting from yeast-induced inflammation in rats and pointed out that DuP 697 took longer to reach its peak activity than did ether piroxicam or indomethacin. In addition, I mentioned that DuP 697 had no activity in chemically-induced acute models of pain in mice; analgesic models in which piroxicam and indomethacin were active.

14. Slide 5, "DuP 697 Antipyretic Activity". Then I described the potent antipyretic activity of DuP 697. It had a lower ED50 than either indomethacin or piroxicam in both rat and mouse models of fever. I mentioned that these data were important for 2 reasons: 1) they indicated in vivo activity in a second species, the mouse and 2) they showed DuP 697 to be active after oral dosing in a relatively short time period. I mentioned that the time to peak antipyretic activity was 2 to 6 hours

for both DuP 697 and indomethacin. I also said that DuP 697 had no effect on the temperature of normothermic animals at doses up to 18 mg/kg.

15. Slide 6, "DuP 697 Safety". With this slide I discussed the wide safety margins DuP 697 had in gastrointestinal and renal models. The gastrointestinal safety was based on both single and multiple dose studies. DuP 697 did not cause ulcers in rats or dogs at single doses of 400 mg/kg or 200 mg/kg, respectively. I reminded the audience that the single dose efficacy in rats was 0.05 mg/kg for antipyretic activity. After 12 days of dosing at 8mg/kg/day, the rats had no adverse gastrointestinal effects. I mentioned that this was a much higher dose than the 0.18 mg/kg/day that was needed for the efficacy in the established adjuvant arthritis model. Likewise in dogs, 14 days dosing at 10mg/kg/day produced no adverse gastrointestinal effects. To specifically examine the safety of DuP 697 in a model that resembled the problems that COX I inhibitors can induce in patients, a volume depleted rat system was used. This model creates the situation where prostaglandins are needed to maintain renal blood flow as a consequence of the low blood volume. COX I inhibitors block the renal production of prostaglandins and the renal blood flow is reduced because of the cyclooxygenase inhibition. Indomethacin at 3 mg/kg i.v. reduced renal blood flow in volume depleted rats. DuP 697 at 5mg/kg/i.v. had no effect on renal blood flow. These results suggested a better safety margin for DuP 697 and indicated a different activity profile than the normal cyclooxygenase inhibitor.

16. Slide 7, "DuP 697 Cellular Activity". With this slide I switched to the *in vitro* activities of DuP 697 starting with cellular systems. In these assays human cells could be used, and the activity evaluated in the same species we hoped to treat. First, human monocytes were stimulated with LPS and incubated overnight. The amount of Prostaglandin E2 made by the cells was measured. Both DuP 697 and indomethacin were very potent as inhibitors of this system. In the second system, human fibroblasts were stimulated with IL-1beta, and the amount of Prostaglandin E2 produced was measured. DuP 697 was very effective and much more potent than indomethacin. In the third system, arachidonic acid was used to cause the aggregation of human platelets. A cyclooxygenase inhibitor such as indomethacin blocks the conversion of arachidonic acid into thromboxane and the platelets do not aggregate. I pointed out that based on the *in vivo* anti-inflammatory activity and the cellular potency in the other 2 systems, DuP 697 would be expected to be equal or better in potency than indomethacin. In contrast it was more than 10 fold less potent than indomethacin at blocking platelet aggregation. I pointed out that platelets contain COX I again suggesting a different profile of activity for DuP 697 than other cyclooxygenase inhibitors.

17. Slide 8, "DuP 697 Enzymatic Activity". I started with the methods used in this slide. For the sheep seminal vesicle assay, radiolabeled arachidonic acid was converted into Prostaglandin products which were separated and measured. In the other 2 assays, microsomal preparations of the organs were prepared and incubated with arachidonic acid. The resulting Prostaglandin E2 was measured using commercial radioimmunoassay kits. I made 2 points with this slide. First, DuP 697 did inhibit cyclooxygenase. Second, it was equipotent with indomethacin as an inhibitor of rat brain cyclooxygenase, but considerably less potent as an inhibitor of either sheep seminal vesicle cyclooxygenase or rat renal cyclooxygenase. I mentioned that similar effects were found using separated kidney cortex and kidney medulla. I suggested that the relative lack of DuP 697 inhibition of kidney microsomal cyclooxygenase may reflect its lack of *in vivo* activity in the volume depleted rat model. I suggested that like the cellular data the enzymatic data indicated selectivity by DuP 697 among cyclooxygenase activities.

18. Slide 9, "DuP 697 Platelet Activity (*in vitro*)" I started this slide by saying that I wanted to focus on the platelet activity for a couple of slides. Here was an activity that could be directly measured both *in vitro* and *in vivo*. For the *in vitro* studies on this slide, human platelet rich plasma was incubated with 3 different agents that caused platelet aggregation: arachidonate, collagen and ADP. Indomethacin was a potent inhibitor of the aggregation induced by the first 2 agents but did not block ADP-induced aggregation as expected from the literature. DuP 697 was a weak inhibitor of platelet aggregation, but equipotent or better than indomethacin in other *in vitro* and *in vivo* models already discussed.

19. Slides 10, "DuP 697 Platelet Activity (*in vivo*)". Next I described the *in vivo* platelet activity model and demonstrated that DuP 697 did not block arachidonate-induced platelet aggregation in mice or rats at orally administered doses much greater than those needed to block yeast-induced fever or adjuvant-induced inflammation in the respective species. I mentioned that the time of arachidonate-induced aggregation evaluation in the mice was the same as the time frame used in the antipyretic study where DuP 697 was active at 0.14mg/kg. I pointed out that indomethacin and ibuprofen both were active in the arachidonate-induced aggregation model at doses similar to those at which they were active in the antipyretic and anti-inflammatory models. Again I suggested a selectivity among the cyclooxygenases with DuP 697 not being very effective against platelet cyclooxygenase (COX I) while it was much more effective against the cyclooxygenase in macrophages, fibroblasts and brain tissue.

20. "DuP 697 Summary". With the summary slide I reiterated the key points of the talk. DuP 697 was active in the standard models as an anti-inflammatory, antipyretic, and in models of inflammatory

pain. I emphasised again the remarkable potency of DuP 697 as it acted like a cyclooxygenase inhibitor in some cellular and enzymatic systems, but that it showed selectivity by lacking potency in other systems. I suggested that the lack of platelet activity may make DuP 697 a safer cyclooxygenase inhibitor because it would not potentiate bleeding. I made the point that the lack of *in vivo* platelet activity together with the gastrointestinal safety profile suggested an *in vivo* selectivity amongst cyclooxygenases. I closed by saying that DuP 697 may be a useful tool for understanding the role of cyclooxygenases I and II.

Properties of DuP 697

21. I have been asked about my reaction to my findings in relation to the properties of the DuP 697 molecule. DuP 697 had been characterized pharmacologically and enzymatically as a selective cyclooxygenase inhibitor. However, the selectivity was difficult to explain because only one cyclooxygenase gene had been described until the work in Simmons' lab with chick fibroblasts and the work from Herschman's lab with mouse 3T3 cells. These studies suggested that there was another gene related to COX I that was inducible and may produce an active cyclooxygenase protein. The activity of DuP 697 in the monocyte and fibroblast cellular assays convinced me that we now had a solid biochemical mechanism for the anti-inflammatory activity of DuP 697 and that we now had a testing paradigm to use for a rapid analoging program around the structure of DuP 697. We needed to keep the activity profile and find an analog with a shorter half-life. I believed that we had the synthetic expertise and assay experience to forge ahead with additional compounds. I certainly thought that DuP 697 should be the starting point for series of analogs and I made this proposal to research management.

22. I have been asked why the DuPont Merck molecule itself was not pursued and developed on. DuP 697 itself had too long a half-life in humans to be practical. I understood that the major objection to my proposal for an analoging program around DuP 697 was the anticipated cost of proving in clinical studies that a COX II inhibitor would be safer than a COX I inhibitor. The burden of proving a compound safer than current compounds with respect to gastric irritation might take over 10,000 patients in the Phase III trials. The expense of such a trial was, I believe, considered prohibitive.

21. I believe that the facts stated in this witness statement are true.

Signed William Galbraith

William Galbraith

Dated August 23, 1999

Served this day of August 1999 by Lovell White Durrant of 65 Holborn Viaduct, London EC1A 2DY, Solicitors for the Defendants

64

Defendants
W Galbraith
First
WG3
Dated: 23 August 1999

1998 M No 1421

IN THE HIGH COURT OF JUSTICE

CHANCERY DIVISION

PATENTS COURT

BETWEEN

(1) MONSANTO COMPANY
(2) G.D. SEARLE & COMPANY
(3) PFIZER INC

Plaintiffs

- and -

(1) MERCK & CO., INC.
(2) MERCK SHARP & DOHME LIMITED

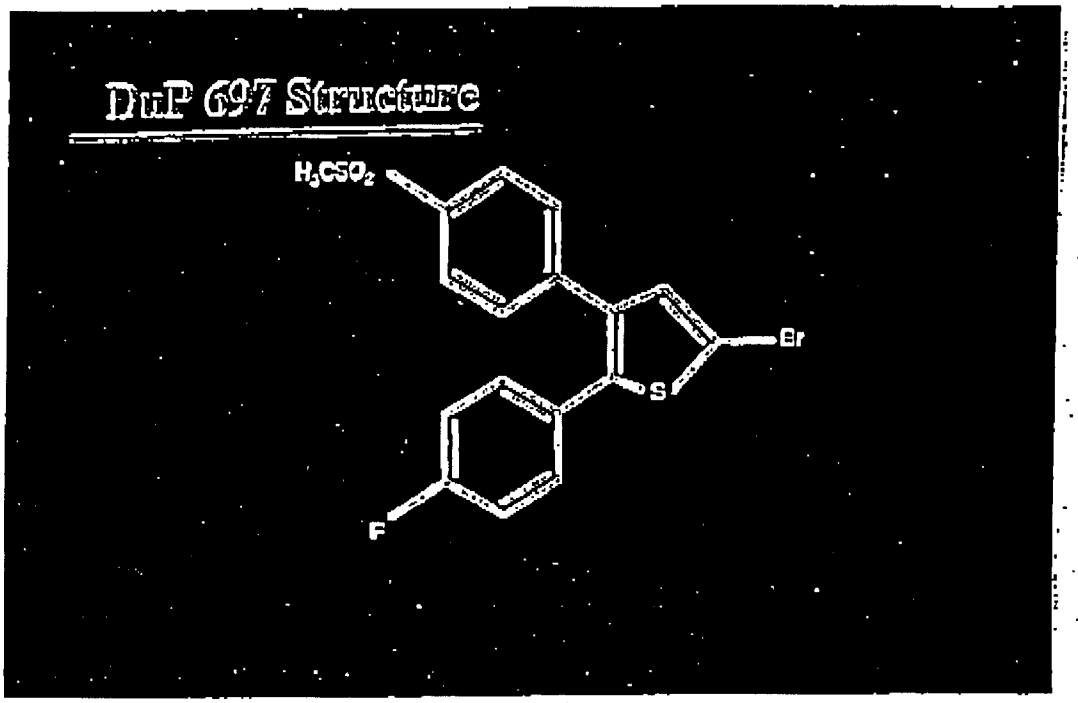
Defendants

EXHIBIT WG3

This is the exhibit referred to as "Exhibit WG3" in the Witness Statement of William Galbraith signed this 23 day of August 1999

William Galbraith

William Galbraith


DuP 697 Structure
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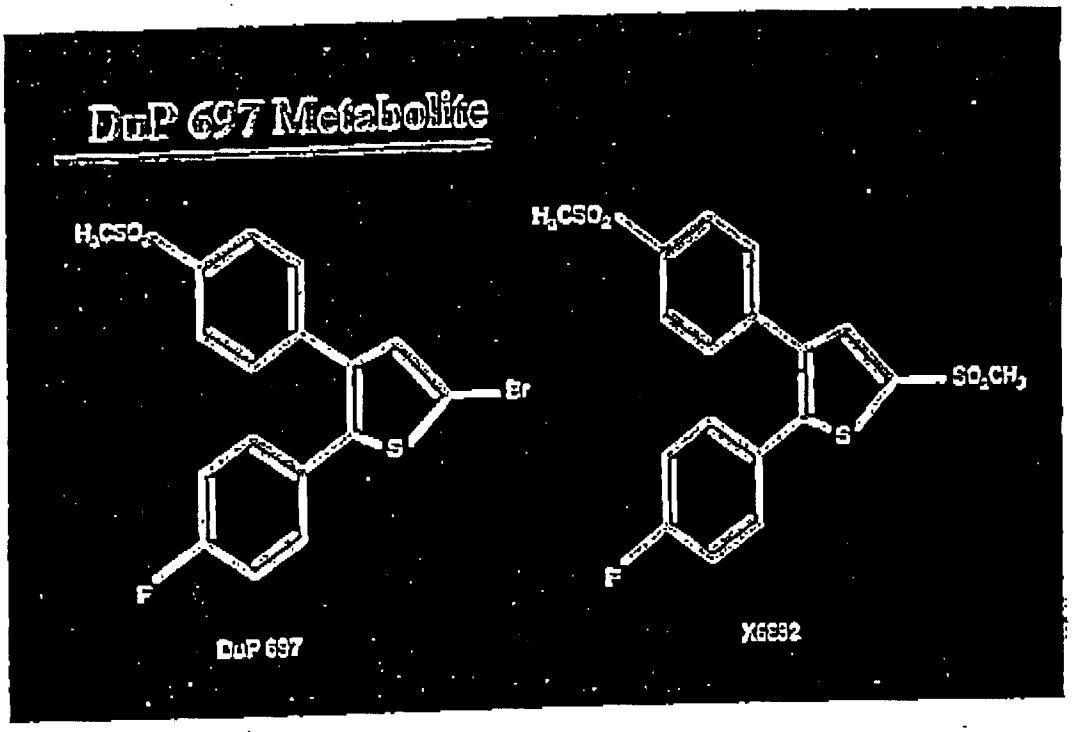
S
F


DuP 697 Metabolite
H_3CSO_2
Br
S
F
DuP 697
H_3CSO_2
SO_2CH_3
S
F
X6832

DuP 697 Anti-Inflammatory Activity

	Adjuvant Arthritis ED 50 mg/kg	
	oelab	non-oelab
DuP 697	0.18	0.03
Indomethacin	0.27	0.05
Piroxicam	0.27	-

DuP 697 Analgesic Activity

	Randall - Selitto Yeast Paw	
	ED 30 mg/kg	peak time
DuP 697	3.5	4+ hr
Indomethacin	1.0	1 - 4 hr
Piroxicam	3.2	1 - 4 hr

DuP 697 Antipyretic Activity

	Yeast-Induced Pyresis	
	ED 50 mg/kg mouse	rat
DuP 697	0.14	0.05
Indomethacin	0.94	0.87
Piroxicam	0.54	2.7

DuP 697 Safety

- Gastrointestinal:
  - rat 1 day >400mg/kg
  - dog 1 day >200mg/kg
  - rat 12 day no effect at 8 mg/kg/day
  - dog 14 day no effect at 10 mg/kg/day
- Renal
  - Volume depleted rat -
  - no effect at 5 mg/kg i.v.
  - indomethacin active at 3mg/kg i.v.

DuP 697 Cellular Activity

	IC50 µM	
	DuP 697	Indomethacin
Human Monocytes (LPS)	0.0018	0.0034
Human Fibroblasts (IL-1)	0.0091	0.082
Human Platelets (AA)	54	3.5

DuP 697 Enzymatic Activity

	IC50 uM	
	DuP 697	Indometh
Sheep Seminal Vesicle	9.6	1.0
Rat Brain Microsomes	4.5	3.8
Rat Kidney Microsomes	62	4.5

DuP 697 Platelet Activity

In Vitro Aggregation 1000 uM

Human PRP	DuP 697	Indometh
Arachidonate	54	3.6
Collagen	13	1.6
ADP	>100	>100

DuP 697 Platelet Activity

In Vivo Arachidonate Protection	ED 50 mg/kg p.o. Mouse	Rat
DuP 697	>81	>50
Indomethacin	0.23	1
Ibuprofen	34	20

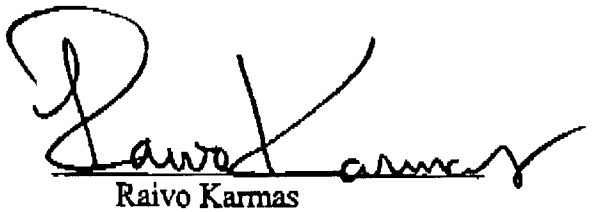
DuP 697 Summary

- Active as an anti-inflammatory, antipyretic and in models of inflammatory pain.
- Evidence of selective inhibition of cyclooxygenase in cellular and enzymatic assays.
- Lack of platelet activity and safety profile may reflect in vivo results of selective CO inhibition.
- May be a useful tool to understand role of cyclooxygenases 1 and 2.

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on December 19, 2005, I caused a true copy of the foregoing **TEVA'S SECOND SUPPLEMENTAL RESPONSE TO PFIZER'S FIRST SET OF INTERROGATORIES (NOS. 1, 3, AND 5-7)** to be served, in the manner indicated, upon the following counsel of record:

BY OVERNIGHT COURIER:	**BY FACSIMILE and BY HAND DELIVERY:**
David E. De Lorenzi GIBBONS, DEL DEO, DOLAN, GRIFFINGER & VECCHIONE A Professional Corporation One Riverfront Plaza Newark, New Jersey 07102	Daniel L. Reisner Kaye Scholer LLP 425 Park Avenue New York, NY 10022-3598 Telephone: 212-836-8000 Facsimile: 212-836-8689
Attorneys for Plaintiffs	*Attorneys for Plaintiffs*



Raivo Karmas